

Thyroid neoplasms: surgical and cyto-histopathological connections on a six year cases study

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SUMMARY: Thyroid neoplasms: surgical and cyto-histopathological connections on a six year case.

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Objective. *This study aims to evaluate the percentage of cyto-histologic correlation in patients with a thyroid disease documented through clinical-instrumental, cytological (FNAB), histological and surgical examinations. The purpose of this study is also to determine the percentage of disease incidence and evaluating any surgical indication in relation to biological behavior (benign, malignant or indeterminate lesions, occult carcinomas), sex, and age.*

Background. *Almost all of thyroid neoplasms is manifested through thyroid nodule. Therefore, clinical evidence of the thyroid nodule analysis is primarily related to the need to exclude malignant pathology*

or carcinoma of the thyroid, present in 4-6.5% of cases.

Patients and methods. *The trial was conducted analyzing the data including cytological and histology thyroid reports recorded from 1 March 2010 to 1 March 2016, for a total of 5,956 reports. To determine the cyto-histological correlations, have been considered eligible all patients of both sexes, that have performed at least one cytologic exam followed by an histologic exam. Thus, the total number of the cases studied is 554 cases.*

Results. *Cyto-histologic compliance was 93% with a diagnostic accuracy of 4% higher than the literature examined.*

Conclusions. *The results thus obtained show, furthermore, that there is a non-negligible percentage of thyroid disease with malignant biological behavior and involvement of male individuals. Therefore, the execution of the FNAB is of utmost importance for the purpose of a correct surgical indication.*

KEY WORDS: Thyroid - Bethesda - TIR - FNAB.

Introduction

Almost all of thyroid neoplasms is manifested through thyroid nodule. Therefore, clinical evidence of the thyroid nodule analysis is primarily related to the need to exclude malignant pathology or carcinoma of the thyroid, present in 4-6.5% of cases (1, 2). Under the appropriate qualification, the best approach is in accordance with the American Thyroid Association (ATA) guidelines and the National Comprehensive Cancer Network (NCCN) guidelines (3, 4). Thyroid nodules acquire clinical relevance when the same patient note enlargement, but also incidentally during a radiological procedure,

such as neck TC, neck RMN, PET or during a routine visit. Nodules that are not palpable (incidentaloma) present the same risk of malignancy of palpable nodules of the same size (5). Furthermore the symptomatology in the elderly is nonspecific and can create a delay in the correct diagnosis (6). A thyroid incidentaloma is an unexpected, asymptomatic thyroid tumor fortuitously discovered during the investigation of an unrelated condition (7). Numerous studies have shown an increase in the incidence of thyroid cancer in recent years (8). The presence of solid component in papillary thyroid carcinoma, regardless of the proportion, is associated with adverse clinical parameters and a shorter disease-free survival (9). Therefore, the initial evaluation of all patients with a thyroid nodule includes: history and physical examination, serum TSH, ultrasound, scintigraphy, fine needle aspiration (FNA), cytological examination, histological examination. Some authors use

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electrical impedance scanning to identify tissue impedance changes associated with malignancy (10).

Aim

The objective of the study is to evaluate the percentage of cyto-histologic correlation in patients with a thyroid disease documented through clinical-instrumental, cytological (FNAB), histological and surgical examinations. The purpose of this study is also to determine the percentage of disease incidence on the population in the study, evaluating any surgical indication in relation to biological behavior (benign, malignant or indeterminate lesions, occult carcinomas), sex, and age.

Patients and methods

Fine-needle aspiration (FNA) has become the predominant method to obtain tissue for microscopic analysis (11, 12). The trial was conducted analyzing the data from surgeries' records (our U.O.C of General Surgery and Urgency makes the largest contribution in terms of number) and from U.O.C of Pathological Anatomy of the University Hospital Policlinic (AOUP "Paolo Giaccone" of Palermo). This database includes cytological and histology thyroid reports recorded from 1 March 2010 to 1 March 2016, for a total of 5,956 reports. To determine the cyto-histological correlations, have been considered eligible all patients of both sexes that have performed at least one cytologic exam followed by an histologic exam. Thus, the total number of the cases studied is 554 cases (Table 1).

With this study we want to express the cytological-histological correlations in case studies and therefore the surgical appropriateness in percentage terms.

We must evaluate, at the same time, the higher incidence of thyroid disease in females, the median age of thyroid disease in subjects of both sexes, biological behavior (benign, malignant or indeterminate), and quantify the incidence of carcinomas occult.

Cases were differentiated according to their membership of specific diagnostic classes according to the Bethesda system (Table 2) (13-16).

Six differentiated cohorts of patients were obtained. Data on patients of Bethesda I diagnostic

TABLE 1 - CASES STUDIED.

Number of patients	554
Middle age	56
Sex	
Male	128
Female	426
Diagnostic classe (histological examination)	
Bethesda I	96
Bethesda II	301
Bethesda III	65
Bethesda IV	26
Bethesda V	58
Bethesda VI	8
Biological behavior (histological examination)	
Benign	360
Malignant	172
Indeterminate	22
Cyto-histological correlations	
Concordance	366
No concordance	27
Occult carcinoma	96

class (non-diagnostic cytology) and Bethesda III diagnostic class (indeterminate cytology) were excluded because cytology is not consistent in these classes. As a result, data on cyto-histologic correlations were obtained on a sample of 393 patients on the 554 of the starting study.

Results

Bethesda I

They were labeled as belonging to the Bethesda I class samples coming from male individuals, in 31.25% of cases, and female subjects, in 68.75% of cases.

TABLE 2 - BETHESDA AND SIAPEC SYSTEMS.

Siapec 2014 Terminology	USA Bethesda 2010 Terminology	Cancer risk
TIR 1 Non-diagnostic for cytological diagnosis TIR 1c (cystic) Unsatisfactory, consistent with cyst	I Non-diagnostic Cystic fluid only	1 to 4%
TIR 2 Benign	II Benign	0 to 3%
TIR 3A Neoplasm possible - atypia/nondiagnostic	III Atypia of undetermined significance or follicular lesions u.s AUS/FLUS	5 to 15%
TIR 3B Neoplasm possible - suggesting follicular neoplasm	IV Follicular neoplasm or suspicious for a follicular neoplasm	
TIR 4 Suspicious of malignancy	V Suspicious of malignancy	60 to 75%
TIR 5 Malignant	VI Malignant	97 to 99%

In 75% of cases, histological examination showed benign lesions (44.4% of cases of adenoma, 55.5% of other benign pathologies), while 23% showed malignant lesions (almost all Cases, 98%, are papillary carcinomas and the remaining 2% of clear cell carcinoma).

Unspecified samples correspond to 2% of the total (100% of cases are of WDT-UMP typology) (Table 3). To note that there is high incidence of papillary microcarcinoma (52.40% of total papillary carcinoma).

Bethesda II

In the 18,6% of cases they were labelled as belonging to the Bethesda II class the samples coming from male individuals, and from female subjects, in 81.4% of cases. In 77.7% of the cases histological examination showed benign lesions (29.9% of cases of adenoma, 70.1% of other benign pathologies), while 18.3% showed malignant lesions (Almost all cases, 96%, are papillary carcinoma, while follicular and medullary carcinoma represent only 2%).

Indeterminate samples correspond to 4% of the total (83.3% of cases are of WDT-UMP type, while the remaining 16.7% are represented by an FT-UMP) (Table 3).

To note that there is high incidence of papillary microcarcinoma (37.7% of total papillary carcinoma).

Cyto-histological concordance was observed in 96% of cases (concordance: 289. No concordance: 12).

Bethesda III

They were labelled as belonging to the Bethesda class III samples coming from male individuals, in 30.7% of cases, and from female subjects, in 69.3% of cases. In 56.9% of the cases histological examination showed benign lesions (64.9% of adenoma cases, 35.1% of other benign pathologies), while 36.9% showed malignant lesions (Almost all cases, 95%, are papillary carcinomas, while the remaining 5% are follicular carcinomas).

Indeterminate samples correspond to 6.2% of the total (100% of cases are of WDT-UMP typology) (Table 3).

Bethesda IV

They were labelled as belonging to the Bethesda IV class samples from male individuals, in 26.9% of cases, and from female subjects, in 73.1% of cases. In 15% of cases histological examination showed benign lesions (75% of adenoma cases, 25% of other benign pathologies), while 73.1% showed malignant lesions. Of these, 73.7% is papillary carcinoma, 10.5% of follicular carcinoma, 10.5% of oncocytic carcinoma and 5.3% of lymphoma. Indeterminate samples correspond to 11.9% of the total (66.7% of

TABLE 3 - TOTAL PATIENTS AND CORRELATION WITH BETHESDA SYSTEM.

Classification	Bethesda I	Bethesda II	Bethesda III	Bethesda IV	Bethesda V	Bethesda VI
Total	96	301	65	26	58	8
Middle age	55,5	56,5	54,6	55,4	53,8	57,7
Sex						
Male	30	56	20	7	11	4
Female	66	245	45	19	47	4
Biological behavior						
Benign	72	234	37	4	12	1
Adenoma	32	70	24	3	8	0
Other	40	164	13	1	4	1
Malignant	22	55	24	19	45	7
Papillary carcinoma	21	53	22	14	37	5
Classical	0	11	4	6	19	5
Microcarcinoma	11	20	8	0	8	0
Capsulated	2	1	0	0	2	0
Follicular	7	19	8	4	7	0
High cells	0	0	0	1	0	0
Widespread sclerosing	0	1	1	1	0	0
Ossifila	0	0	1	1	1	0
Solid	0	0	0	0	0	0
Cribriform	0	1	0	1	0	0
Clear cells	1	0	0	0	0	0
Follicular carcinoma	0	1	2	2	1	0
Oncocytic carcinoma	0	0	0	2	2	0
Clear cells carcinoma	1	1	0	0	1	0
Poorly-differentiated carcinoma	0	0	0	0	3	1
Anaplastic carcinoma	0	0	0	0	0	0
Medullary carcinoma	0	1	0	0	1	1
Other	0	0	0	1	0	0
Indeterminate	2	12	4	3	1	0
WDT-UMP	2	10	4	2	1	0
FT-UMP	0	2	0	1	0	0

cases are WDT-UMP type and the remaining 33.3% are FT-UMP) (Table 3). Cyto- histological concordance was observed in 88,5% of cases (concordance: 23. No concordance: 3).

Bethesda V

They were labelled as belonging to the class Bethesda V samples coming from male individuals, in 18.9% of cases, and from female subjects, in 81.1% of cases. In 20.7% of cases histological examination showed benign lesions (66.6% of adenoma cases, 33.4% of other benign pathologies), and 77.6% showed malignant lesions. Of this type, 82.2% describes a papillary carcinoma, 2.2% a follicular, 2.2% a clear cell carcinoma, 2.2% a medullary carcinoma, 4.5% a carcinoma Hurthle

cells and 6.7% a poorly differentiated carcinoma.

Indeterminate samples correspond to 1.7% of the total (100% of cases are of WDT-UMP typology) (Table 3).

Cyto- histological concordance was observed in 89% of cases (concordance: 47. No concordance: 11).

Bethesda VI

They were labelled as belonging to the class Bethesda VI samples coming from male individuals, in 50% of cases, and from female subjects, in 50% of cases. In 12.5% of the cases histological examination showed benign lesions (100% of cases of adenoma), while 87.5% showed malignant lesions.

Of these samples, 71.4% describe papillary carci-

noma, 14.3% a poorly differentiated carcinoma, and 14.3% a medullary carcinoma (Table 3).

Cyto- histological concordance was observed in 87,5% of cases (concordance: 7. No concordance: 1).

Discussion

Thyroid FNA is a safe and reliable procedure for cytological assessment of thyroid nodules (17). In female subjects, this tumor is globally in the fourth rate in incidence (5% of all cases) and represents 5% of the total number of tumors occurring between 50-69 years of age (18, 19).

Thyroid nodules with repeated Bethesda category III classification and irregular/microlobulated margins on US are at increased risk of malignancy, and operative management should be considered as opposed to repeat FNA (20).

Cases with cyto-histologic correlations diagnosed in Italy in 2007-2011 correspond to 98% of the total. Among malignant neoplasms, 84% is papillary histological type, 8% follicular, 3% medullary, 1% anaplastic form, the remaining part of other and non-specified morphologies (18). In our study cyto-histologic correlations was observed in 93% of the total cases. Among malignant neoplasms: 88.4% is papillary histological type, 3.5% is follicular, 1.7% is medullary, 2.3% is Hürtle histological type, 1.1% is light cell histological type, 2.3% is insular histo-

logical type and 0.8% is lymphoma. There are 160,307 patients resident in Italy with pre-diagnosed thyroid cancer, including 78% women (19). The proportion of prevalent cases is higher in the age groups 45-59 (143/100,000 among men and 497/100,000 among women) and 60-74 years (161/100,000 among men and 521/100,000 among women). There are moderate differences between the different areas of the country: men and women have, in fact, proportions of 78 and 234 cases/100,000 in NO, 95 and 317 in NE, 100 and 338 in the Center, 85 and 315 in the South (19). Our study shows that the average age of patients is 56 years. Of all patients, 23.1% are males and 76.9% women. It is also apparent from the trial that although thyroid disease is less likely in the male, the likelihood of malignant cytotoxicity following the execution of an FNAB is higher; actually, male cases belonging to the Bethesda II diagnostic class (cytology of benignity) represent 18.6% versus 50% of Bethesda VI (cytologic diagnosis of certain malignancy). A comparison was made between the data obtained from our study (Study A) and data from the literature “The Bethesda System for Reporting Thyroid Cytopathology: A Meta-Analysis” of 2012 (Study B) (Table 4) (21). This meta-analysis was conducted on a cohort of 25,445 thyroid neoplasms, 25% of which (6,362) were followed by surgical excision. The diagnostic accuracy was 68.8% versus 93% obtained in Study A. Comparisons were made between the diagnostic classes belonging to (Table 5).

TABLE 4 - PERCENTAGE OF 6.362 WITH FOLLOW-UP (A). SURGICAL CASES IN EACH CATEGORY (B). TOTAL SURGICAL CASES IN EACH CATEGORY (C).

Cytological Diagnosis	All FNAs n	All FNAs % tot	All FNAs with histological follow-up n	All FNAs with histological follow-up % tot (A)	All FNAs with histological follow-up % category (B)	Benign histology n	Benign histology % (C)	Malignant histology n	Malignant histology % (C)
Nondiagnostic	3,271	12.9	530	8.3	16.2	441	83.2	89	16.8
Benign	15,104	59.3	1,563	24.6	10.4	1,505	96.3	58	3.7
AUS/FLUS	2,441	9.6	957	15.0	39.2	805	84.1	152	15.9
FN/SFN	2,571	10.1	1,791	28.2	69.7	1,323	73.9	468	26.1
Suspicious for malignancy	680	2.7	501	7.9	73.7	124	24.8	377	75.2
Malignant	1,378	5.4	1,020	16.0	74.0	14	1.4	1,006	98.6
Total	25,445	100	6,362	100	25.0	4,212	66.2	2,150	33.8

TABLE 5 - COMPARISONS BETWEEN THE DIAGNOSTIC CLASSES.

Diagnostic class	Study A	Study B
Bethesda I	17.3%	12.9%
Bethesda II	54,4%	59.3%
Bethesda III	54,4%	9,6%
Bethesda IV	4,7%	10,1%
Bethesda V	10,7%	2,7%
Bethesda VI	1,4%	5,4%

Significant differences were found in the Bethesda IV, V and VI classes, while for the remaining classes the range is almost overlapping. Consequently, in study A there is a lesser trend of the anatomy-pathologist to classify cytological examination as a follicular neoplasia (Bethesda IV), whereas the diagnosis of suspected malignancy (Bethesda V) is more prevalent. In the table, comparisons were made of malignant biological behavior (Table 6).

In relation to the predictive value of malignancy and the consequent need for surgical intervention, significant diagnostic percentages in Bethesda II, III and IV classes were shown in Study A, while for the remaining classes the range is almost overlapping. The difference of 14.6 percentage points between study A and study B data on the Bethesda II category (cytology of benignity) is likely to be attributed to the high incidence of occult carcinomas in the context of benign thyroid disease in study A (approximately 6.6% of all Bethesda II cases). Comparisons were made of benign biological behavior (Table 7).

Concerning the predictive value of benignity in Study A, significant diagnostic results were reported in the Bethesda III, IV, V and VI classes. In the Bethesda III diagnostic class (cytological diagnosis of indeterminate lesion), study A showed less benign biological behavior than study B. A substantial difference was found in the cytologic class Bethesda IV (cytologic diagnosis of follicular neoplasia). In the diagnostic classes Bethesda IV and Bethesda V (cytological diagnosis of suspected malignancy) it can be noted that in study A, following a cytological examination suspected of malignancy, there was indeed a lower the finding of benign pathology at post-surgical histology. The opposite situation,

TABLE 6 - COMPARISONS BETWEEN BENIGN AND MALIGNANT BIOLOGICAL BEHAVIOR.

Diagnostic class	Study A	Study B
Malignant behavior		
Bethesda I	23%	16,8%
Bethesda II	18,3%	3,7%
Bethesda III	36,9%	15,9%
Bethesda IV	73,1%	26,1%
Bethesda V	77,6%	75,2%
Bethesda VI	87,5%	98,6%
Benign behavior		
Bethesda I	75,1%	83,2%
Bethesda II	77,7%	96,3%
Bethesda III	56,9%	84,1%
Bethesda IV	15%	73,9%
Bethesda V	20,7%	24,8%
Bethesda VI	12,5%	1,4%

however, occurs in the Bethesda VI diagnostic class (cytologic diagnosis of certain malignancy). In this class, it can be noted that in study A, following a cytological examination that referred to certain malignancy, there is a higher rate of benign histology following thyroidectomy surgery. It should be emphasized that study A has a very small cohort of patients belonging to the Bethesda VI diagnostic class (8 patients). Of these 8, only one case was benign, therefore the percentage is 12.5%, but on a cohort of very small patients.

Some Authors affirm that nodules subject to FNA show step-wise decline in malignancy rates by size, demonstrating that size alone should not be considered as an independent risk factor (22).

Conclusions

Cyto-histologic compliance was 93% with a diagnostic accuracy of 4% higher than the literature examined (21). There is considerable practice varia-

TABLE 7 - SONOGRAPHIC PATTERNS, ESTIMATED RISK OF MALIGNANCY, AND FNA GUIDANCE FOR THYROID NODULES.

Sonographic pattern	US features	Estimated risk of malignancy	Consider biopsy (FNA size cutoff, largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule WITH one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension	>70 to 90%	Recommend FNA at >1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins WITHOUT microcalcifications, extrathyroidal extension, or taller than wide shape	10 to 20%	Recommend FNA at >1 cm
Low Suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, WITHOUT microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape	5 to 10%	Recommend FNA at >1.5 cm
Very low Suspicion	Spongiform or partially cystic nodules WITHOUT any of the sonographic features described in low, intermediate, or high suspicion patterns	<3%	Consider FNA at >2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1%	No biopsy

tion in thyroid testing which suggests a need for better guidance in test selection (23).

Incidental thyroid carcinomas are not uncommon. Multifocality and bilaterality are often present such as occult lymph node metastasis. Therapeutical choice is total thyroidectomy and follow-up (24). Total thyroidectomy remains the safest treatment in differentiated thyroid cancer (25).

It is therefore desirable in the future to increase cooperation between the various healthcare institutions, to refine the most modern imaging techniques, and to check on the accuracy of the results in order to be able to align to national 98% ISTAT (18). The results thus obtained show that there is a

non-negligible percentage of thyroid disease with malignant biological behavior and involvement of male individuals. Therefore, it is imperative for the physician to comply with the appropriate procedure to make a timely and correct diagnosis (Table 7) (3, 26).

In addition, because of the high incidence of occult carcinomas, it is recommended for patients with benign thyroid pathologies to continuously monitor the gland (27-30).

The collaboration between endocrinologists and surgeons in a multidisciplinary frame is the key to correct preoperative thyroid cancer diagnosis and optimal treatment (31, 32).

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